

## Comparison of Cognitive Impairment between Patients having Epilepsy and Psychogenic Nonepileptic Seizures

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### ABSTRACT

**Introduction:** The aim of this study was to evaluate cognitive impairment in patients having epilepsy or psychogenic nonepileptic seizures (PNESs) using selected neuropsychological tests at different time periods related to the seizure.

**Methods:** In this study, selected neurocognitive tests were administered to the patients. Within 24 h, the previously applied neurocognitive tests were repeated within 24 h following the observation of typical seizures when monitoring and normalizing electroencephalography (EEG) activity. Basal neurocognitive tests were also administered to the healthy control group, and repeat neurocognitive evaluation was performed within 24–96 h.

**Results:** The basal neurocognitive evaluation revealed that verbal learning and memory scores as well as Stroop test interference time were significantly lower in the PNES group compared with those in the controls. In the basal cognitive tests administered to the patients with

epilepsy, verbal learning and memory scores, long-term memory, and total recognition test scores were significantly lower than those of the controls. Following the repeat cognitive tests, significant progress was found in the verbal categorical fluency score of the PNES group. No significant difference was determined in the epilepsy group. Significant contraction was determined in the Stroop interference time in the control group, but no similar change was recorded in the epilepsy or PNES groups.

**Conclusion:** While memory problems seemed to be most prominent in the assessed patients with epilepsy, attention and executive function problems were more dominant in the patients with PNESs. These findings are probably related to numerous factors such duration of disease, mood disorders, and specific drug use. No deterioration in attention and executive functions was reported in the early post-seizure period in either patient group.

**Keywords:** Psychogenic nonepileptic seizure, epilepsy, cognition

### INTRODUCTION

Epileptic seizures are self-limiting, abnormal, hyper-synchronized discharges of cortical neurons. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition (1). Psychogenic nonepileptic seizures (PNESs) are a condition resembling epileptic seizures but are not accompanied by a physiological disorder (2). They are classified among dissociative disorders in International Classification of Diseases-10 (ICD-10) and somatoform disorders in the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (3,4). Up to 20–30% of patients referred to epilepsy centers with a diagnosis of epilepsy have been shown to have been misdiagnosed (5,6). PNESs occupy the first place among misdiagnosed conditions (7).

For many years, it has been debated and investigated whether epileptic activity causes damage in the brain. Many longitudinal cognitive studies with adult patients with epilepsy have been performed to investigate this complex problem. As a result of these studies, a marked loss of mental abilities has been shown in epilepsy patients with uncontrolled seizures (8). Factors such as seizure etiology, age and onset of seizures, frequency of seizures, type of seizure, duration of disease, and location of the lesion leading to epilepsy if any are responsible for the effect of epilepsy on test performance. Lesion localization is directly correlated with an expected neuropsychological disorder in symptomatic epilepsies (9).

Although it has been suggested that because of the organic nature of epilepsy, patients with epilepsy will exhibit greater impairment in neuropsychological tests compared to those with PNESs, some studies have reported no difference, whereas other studies have reported a greater effect in patients with epilepsy and others have reported a greater effect in patients with PNESs at cognitive assessments (10).

The purpose of this study was to evaluate the cognitive impairment of patients with epilepsy and PNESs using selected neuropsychological tests before the seizure and in the early period post-seizure. We intended to assess the cognitive status in both patient



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groups, especially pre-seizure, and subsequently to evaluate the cognitive effects that persist despite epileptic activity observed at surface electroencephalography (EEG) after the seizure returns to normal in patients with epilepsy, and the probable cognitive effects developing after the dramatic dissociative process in patients with PNESs.

**METHODS**

The study was approved by the ethical committee of Dokuz Eylül University. Patients attending the Epilepsy and Sleep Disorders Clinic and who were indicated for video EEG monitoring were assessed for the study. Twenty healthy controls were also included.

Epilepsy was defined according to International League Against Epilepsy criteria (clinical findings and EEG and/or video EEG). Nonepileptic psychogenic attacks were defined as clinically observed atypical paroxysmal movements or sensations and the concurrent absence of pathological EEG activity. Patients scheduled for inclusion in the study were informed about the tests to be performed. All patients were read a consent form to the effect that they were participating voluntarily, and patients who signed the form were duly enrolled.

Following admission to hospital, the patients were assessed using the Mini International Neuropsychiatric Interview (MINI), and patients with at least 8 years of education were included in the study. Patients with a history of brain damage and psychotic disorder at the DSM-IV axis I diagnosis were excluded. The healthy control group consisted of age- and education level-matched volunteers.

Forty patients and 20 controls were initially included in the study. One patient was excluded because of psychotic findings following the MINI interview. Four patients were not analyzed because no typical seizure was observed during their hospitalization. Findings from one patient were compatible with non-REM parasomnia. PNESs and epileptic seizures were observed together in three patients, and these patients were also excluded. Of the remaining 31 patients in the study, PNESs were observed in 20 and epileptic seizures in 11. Partial seizures were observed in all patients with epilepsy and secondary generalization in all seizures. Left frontal focus was present in three patients and temporal focus in eight (right/left: 5/3). Group demographic data are given in Table 1. The cranial images of patients with epilepsy were retrospectively analyzed. Data for two patients were unavailable. At the cranial magnetic resonance imaging (MRI) of the other patients, findings compatible with left hippocampal sclerosis were determined in two patients, and atrophy and increased intensity in the bilateral hippocampal regions were observed in one. The cranial MRI of six patients was assessed as normal.

Seizure semiology in the patients with PNES was evaluated on the basis of the modified PNES subgroup classification Griffith et al. (11). The patients were divided into two groups on the basis of their semiologies. The “minor motor” group consisted of patients who remained motionless and unresponsive to external stimuli for a prolonged period or in whom low amplitude movements were observed in the face or extremities or in whom consciousness was maintained and who were able to report sensory and emotional experiences. The “major motor” group consisted of patients with asynchronous movements in the extremities or in whom unusual behavior was observed (nodding, kicking, shouting, etc.). Patients with more than one seizure and both major and minor seizure semiologies were classified in the major motor group. Of the 20 patients diagnosed with PNES, 10 were included in the minor motor group and 10 in

**Table 1.** Demographic data

		PNES (n=20)	Epilepsy (n=11)	Control (n=20)
Number (n)		20	11	20
Gender	Female	18	4	15
	Male	2	7	5
Marital status	Married	11	2	12
	Single	9	9	8
Employment	Working	13	6	20
	Not working	7	5	20
Mean age (years)		28.85±8.99	28.82±13.14	31.05±6.985
Education level (years)		11.10±2.33	9.55±2.16	11.20±2.28
PNES: psychogenic nonepileptic seizure				

The patients included in the study were administered the following basal neurocognitive tests: the Öktem Verbal Memory Processes Test (VMPT), verbal categorical fluency test, and number sequencing tests. The neurocognitive tests previously administered to the patients were repeated within 24 h of the observation of typical seizures at monitoring and of EEG activity returning to baseline. The basal neurocognitive tests were also administered to the healthy control group with repeated neurological evaluation performed within 24–96 h. The word groups were altered in VMPT to reduce the learning effect in both groups.

The patients were also assessed for accompanying depression, because we foresaw that this may affect cognition, using the Hamilton Rating Scale for Depression (HRSD) and were evaluated in terms of duration of disease and frequency of (Table 2).

Both patient groups were also evaluated in terms of antiepileptic drug use.

**Statistical Analysis**

Study data were analyzed using Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) for Windows (Release 15.0). Fisher’s exact test was used for categorical/two-way variables in independent groups and the Mann–Whitney U test Kruskal–Wallis analysis of variance for numerical/constant variables. The Wilcoxon signed-rank test was used to analyze dependent variables. Spearman’s rank difference correlation was used in the analysis of correlations between variables. Statistical significance was set at p<0.05 for all analyses.

**RESULTS**

**Basal Cognitive Assessment Results**

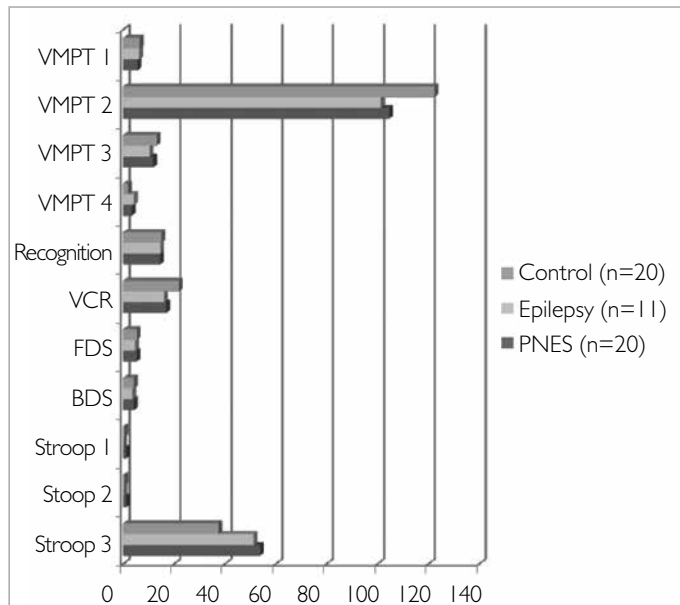
At basal cognitive assessment, the VMPT learning scores and Stroop test interference time were significantly poorer in the PNES patient group compared with the control group (p=0.023, p=0.026). The VMPT learning scores, long-term memory, and total recognition and verbal categorical fluency test scores were significantly lower in patients with epilepsy compared with those of the controls (p=0.012, p=0.003, p=0.005, and p=0.015, respectively) (Figure 1).

When the patients’ basal cognitive test results were compared, the patients with epilepsy exhibited a worse performance in VMPT learning, VMPT long-term memory, and verbal categorical fluency and digit span tests compared to those of the patients with PNES, although the differences were not significant.

**Table 2.** Data concerning disease duration, seizure frequency/duration and age at onset of disease

	PNES (n=20)	Epilepsy (n=11)	p
Duration of disease (years)	4.21±5.13	10.18±10.38	0.031
Frequency of seizure (months)	11.70±9.23	14.45±11.09	0.573
Duration of seizure (minutes)	8.30±12.77	1.72±1.10	0.002
Age at onset of disease (mean)	24.65±8.21	18.82±12.58	0.021

PNES: psychogenic nonepileptic seizure

**Figure 1.** Basal cognitive assessment

VMPT 1: verbal memory processes test immediate memory score; VMPT 2: verbal memory processes test learning score; VMPT 3: verbal memory processes long-term memory; VMPT 4: verbal memory processes recognition; Recognition: total recognition; VCR: verbal categorical fluency; FDS: forward digit span; BDS: backward digit span; Stroop 1: Stroop test error number; Stroop 2: Stroop test spontaneous correction; Stroop 3: Stroop test interference time; PNES: psychogenic non-epileptic seizure

Subgroup analysis of the basal cognitive test results of the patients with PNES classified into major and minor motor semiological groups revealed no significant difference between them. On account of the low patient numbers involved, the semiological subgroup cognitive test results could not be compared within groups among the patients with epilepsy. However, compared with the control group, the patients with epilepsy having temporal focus had low VMPT learning, long-term memory, and total recognition and verbal categorical fluency scores ( $p=0.032$ ,  $p=0.005$ ,  $p=0.023$ , and  $p=0.044$ , respectively), similar to the previous results.

In terms of the association between basal cognitive data and duration of duration and frequency of attacks, a significant correlation was obtained between disease duration and the VMPT immediate learning and learning scores and disease duration in the patients with epilepsy ( $r=-0.665$ ,  $p=0.026$ ,  $r=-0.653$ ,  $p=0.029$ ). In the patients with PNES, significant correlations were obtained between disease duration and the VMPT immediate learning score and Stroop test interference time ( $r=-0.628$ ,  $p=0.003$ ,  $r=-0.520$ ,  $p=0.19$ ). No correlation was obtained between attack frequency and the cognitive test results.

No significant difference was obtained in either patient group when correlation between age at onset of disease and cognitive test scores was assessed using Spearman correlation analysis.

When the cognitive test results of the patients with mesial temporal sclerosis were compared with those of the other patients with epilepsy, their VMPT immediate learning, VMPT long-term memory, animal list, forward digit span task, and Stroop interference scores were lower, although the differences were not significant.

### Repeat Cognitive Test Results

At the repeat tests, a significant rise was determined in the verbal categorical fluency score of the patients with PNES. No difference was determined in the epilepsy patient group. In the control group, we determined a significant shortening in the Stroop interference time, although no comparable change was observed in the epilepsy or PNES patient groups (Table 3).

### Effect of Antiepileptic Drugs on Cognitive Assessment

When drug use was assessed, we observed that all patients with epilepsy received multidrug therapy (2–4 different antiepileptic drugs); that the most frequently used drugs were valproic acid (500–1750 mg/day), levetiracetam (1000–2500 mg/day), and carbamazepine (800–1200 mg/day); that four patients were receiving topiramate therapy; and that barbiturate species with marked cognitive side-effects were not used. Fifteen patients with nonepileptic seizures were monitored with antiepileptic treatment, with eight of these patients receiving multi-antiepileptic therapy (2–4 antiepileptic drugs) and seven receiving monotherapy. The most common drug for monotherapy was carbamazepine (400–1200 mg/day). Homogeneity could not be established because of multiple drug use and low patient numbers, and subgroup analyses could not be performed.

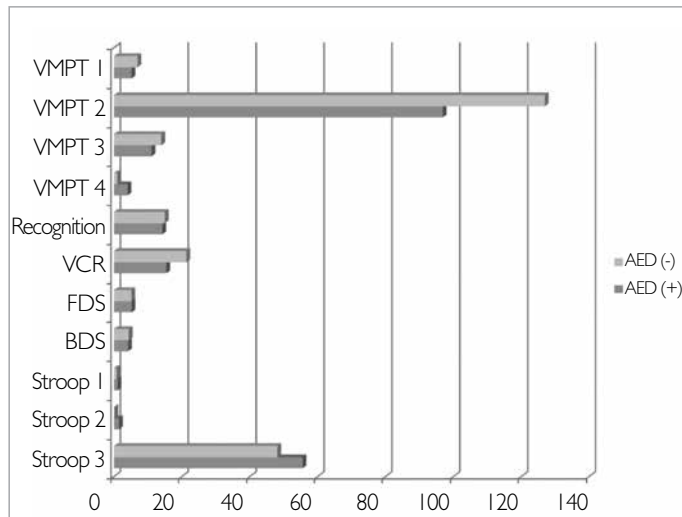
The patients with PNES receiving or not receiving antiepileptic drug therapy were assessed in terms of effects in the basal cognitive tests (Figure 2). All patients receiving treatment exhibited a poorer performance at all assessments, and the difference between the VMPT learning scores, VMPT recognition scores, and verbal categorical fluency scores were statistically significant ( $p=0.016$ ,  $p=0.044$ , and  $p=0.026$ , respectively). No significant differences were determined between these groups in terms of HRSD scores and disease duration.

### Effect of Mood on Cognitive Tests

Patients' mood was assessed using HRSD. The total HRSD scores of both patients with epilepsy and those with PNES were significantly higher compared with those of the controls ( $p=0.001$  and  $p=0.000$ , respectively). In contrast to the patients with epilepsy, however, the HRSD scores in the patients with PNES were above the depression cut-off point. When the relation between the VMPT learning score and HRSD score in the PNES group was assessed using Spearman's rank difference correlation analysis, a negative significant correlation was determined ( $r=-.563$ ,  $p=0.010$ ). No similar correlation was determined in the patients with epilepsy ( $r=-.130$ ,  $p=0.704$ ). A similar significant correlation was determined in the PNES patient group between the Stroop interference period and HRSD score ( $r=-.566$ ,  $p=0.09$ ). Again, no similar correlation was identified in the patients with ( $r=-.147$ ,  $p=0.667$ ).

## DISCUSSION

Most of the patients in the PNES group of our study consisted of women. A moderate higher predominance of females was determined compared with those in previous studies (12). We think that the relatively low level of males determined may be attributed to males seeking less medical assistance because of the sociocultural structure of society. The patients with PNES and those with epilepsy were observed to be less involved in occupational life. The loss of functionality was determined as compatible with the decrease in functional capacity determined using quality of life scales in previous studies (13,14,15).



**Figure 2.** Cognitive effects of antiepileptic drugs in patients with PNES. VMPT 1: verbal memory processes test immediate memory score; VMPT 2: verbal memory processes test learning score; VMPT 3: verbal memory processes long-term memory; VMPT 4: verbal memory processes recognition; Recognition: total recognition; VCR: verbal categorical fluency; FDS: forward digit span; BDS: backward digit span; Stroop 1: Stroop test error number; Stroop 2: Stroop test spontaneous correction; Stroop 3: Stroop test interference time; PNES: psychogenic non-epileptic seizure

The mean age of the patients with PNES diagnosed following admission to our institution was compatible with that in literature at 28.85±8.99 years (16,17,18).

The duration of disease of the patients with epilepsy was longer than that of those with PNES. We think that the longer duration of disease in patients with epilepsy is due to fact that the patients with epilepsy who were admitted largely comprised resistant patients. The duration of disease of the PNES patient group was also assessed as time to diagnosis. A mean diagnosis delay of 7.2±9.3 years has been reported in previous studies, and there was a similar delay in our study (16,19). No significant difference was obtained between the two groups in terms of attack frequency. We expected the frequency of seizures to be higher in the PNES patient group, and we attributed the expected difference not being observed to the patients with epilepsy in this study being resistant. The duration of PNES was significantly longer in agreement with that in literature (20).

Compared with the control group, the VMPT learning and verbal categorical fluency scores were lower in the PNES patient group, and the Stroop interference time was longer. In the patient group diagnosed with epilepsy, the VMPT long-term memory and total recognition scores and categorical verbal fluency values were lower compared with those of the controls. The test results were interpreted as representing a compromise of memory and attention processes in the PNES patient group and a compromise of memory processes in the epilepsy patient group. Although the difference between the two groups was not statistically significant, the VMPT learning score, VMPT long-term memory, categorical verbal fluency test, and digit rank test results were relatively lower in the epilepsy group, and the interference duration was shorter. We concluded from these results that the attention processes were relatively protected in the patients with epilepsy but that the memory processes were affected in the patients with epilepsy in our study, whereas a compromise of attention processes was marked in the patients with PNES.

The data from studies performed to date concerning cognitive effects in patients with epilepsy and those with PNES are not consistent. Prigatano et al. (21) determined lower long-term memory and number-sequencing

**Table 3.** Assessment values between repeated cognitive tests

		PNES (n=20)	Epilepsy (n=11)	Control (n=20)	P
VMPT immediate learning score	1.	5.70±1.92	6.27±1.61	6.50±2.64	0.306
	2.	5.70±2.10	5.63±2.20	6.50±2.09	
VMPT learning score	1.	104.45±25.39	101.18±22.32	122.35±14.74	0.564
	2.	106.70±21.79	102.54±23.76	122.25±13.77	
VMPT long-term memory	1.	11.85±3.45	10.36±2.97	13.10±1.77	0.817
	2.	11.80±2.37	10.36±3.17	12.90±1.48	
VMPT recognition	1.	3.30±3.64	4.18±2.52	1.85±1.75	0.960
	2.	3.05±2.06	4.00±2.60	2.00±1.33	
Total recognition	1.	14.45±4.75	14.54±0.68	15.00±0.00	0.468
	2.	14.85±0.48	14.36±1.50	14.95±0.22	
Verbal categorical fluency	1.	16.95±5.40	16.09±5.94	21.80±4.84	0.008
	2.	20.50±4.00	16.81±5.30	21.45±5.07	
Forward digit span	1.	5.25±1.06	4.72±1.19	5.35±1.13	0.985
	2.	5.20±1.39	4.81±1.07	5.55±1.09	
Backward digit span	1.	4.25±1.33	3.63±0.92	4.20±1.15	1.000
	2.	4.05±1.31	4.00±1.48	4.40±1.46	
Stroop test error number	1.	1.05±2.06	0.09±0.30	0.45±1.05	0.572
	2.	0.75±2.89	0.45±1.50	0.10±0.30	
Stroop test spontaneous correction	1.	1.20±2.21	0.18±0.60	0.45±0.88	0.916
	2.	0.85±1.30	0.63±1.56	0.70±1.08	
Stroop test interference	1.	53.75±24.57	51.27±27.37	37.45±12.47	0.029
	2.	45.45±30.07	44.00±28.11	28.85±11.37	

(1) Basal cognitive tests, (2) Repeat cognitive tests  
 PNES: psychogenic nonepileptic seizure; VMPT: verbal memory processes test. Values given as mean±standard deviation

scores in patients with epilepsy compared to those with PNES. However, the values did not reach statistical significance. These data are compatible with those from our study. The authors suggested that the effect on both attention and memory processes in patients with epilepsy is greater than that in patients with PNES. Strutt et al. (22) reported that a PNES patient group exhibit a better performance in neuropsychological tests compared with patients with epilepsy but that scores are below normal in the attention and executive function tests. In our study, too, and in support of that research, the VMPT immediate learning scores were lower and the Stroop test error number and interference time were longer in the patients with PNES compared to those with epilepsy. However, the difference did not reach statistical significance.

In contrast to the expected compromise in the repeat tests, we determined a significant increase in the categorical verbal fluency score in the PNES patient group. Studies to date have suggested that the low scores determined among patients with PNES in cognitive tests are associated with patients making an insufficient effort during the tests because of which cognitive test results may not be reliable. There are data attributing this inadequate effort to deliberate error in a very small number of patients (feigned sickness) and to the involvement of psychological inadequacy, physical fatigue, and emotional stress in the etiology in a wider patient group (23). In light of these studies, we think that the increase in the re-

peat test scores of the patients with PNES were associated with unreliable test results and that the patients' sleep disturbances may also be associated with stressors being removed in their daily lives during hospitalization. However, further studies are needed to arrive at a definitive conclusion.

Studies to date have determined a greater deficit in verbal memory performance in patients with mesial temporal lobe epilepsy and a longer disease history compared to those with other types of epilepsy, irrespective of the lateralization of focus (24,25). Prefrontal lobe lesions frequently present with executive function impairment and difficulties in fluency, planning, mental flexibility, and complex problem solving (9). Patients with both frontal and temporal origin seizures were included in this study. However, because of the low patient number in the epilepsy group, no comparison was possible between the patients with frontal and temporal origin seizures. Data for temporal focus patients were compared with those of the controls, and an effect on verbal memory was determined, in agreement with previous studies.

Black et al. (26) assessed patients with epilepsy and those with PNES in terms of age at onset of disease and seizure burden. They showed that early age at onset and a high lifetime burden lead to greater cognitive disorder in both groups. However, the cognitive effect is in different areas in the groups; in patients with PNES, a compromise was observed in the attention and executive process, whereas in patients with epilepsy, a compromise was observed in the verbal learning processes. In our study, however, no correlation was determined between age at onset and cognitive effect. Because the range of age at onset in our patient group was relatively narrow, the data were analyzed within a restricted age group. The negative correlation between age at seizure onset and cognitive response shown in other studies may not have been determined for that reason. Lifetime seizure burden was not analyzed in this study. The association between mean seizure frequency and cognitive impairment was assessed, and no significant correlation was determined. Some studies have shown a reverse correlation in patients with epilepsy and those with PNES between disease duration and verbal memory performance (27). Similarly, in our study, we found a correlation between memory performance and disease duration in both patients with epilepsy and those with PNES. However, in the patients with PNES, there was also a negative correlation between disease duration and attention and executive processes. However, the short-term effects of epilepsy seizures were not investigated in detail. No decrease was recorded in the repeat test scores in the early postictal period in our study, although the contraction in the Stroop interference time in the controls was not observed in the patient group. This finding may reveal a compromise of learning and attention processes. The existing data are insufficient for such a conclusion.

In the same way that seizures have adverse effects, specific antiepileptic drugs also have known cognitive side-effects (28). Carbamazepine, valproate, and phenytoin have similar effects on cognitive performance, although phenobarbital has been shown to have a relatively more marked adverse effect (28,29). Among the new antiepileptics, topiramate has marked side-effects, such as lowered concentration, impairment in verbal tests and "dizziness" (30). Patients receiving multiple antiepileptic therapy are at a greater risk of cognitive impairments (31).

Although treatments were interrupted during the patients' hospitalization in the video monitoring unit, the long-term effects of antiepileptic drug use remained an uncontrollable variable. All our epilepsy patients received antiepileptic therapy. However, the patients with PNES who received or did not receive antiepileptic therapy were compared in terms of effects in the basal cognitive tests, and the VMPT learning score and VMPT recog-

nition and categorical verbal fluency scores were significantly higher in the patients not receiving therapy. Because other variables, such as the HRSD scores, affecting cognitive functions in the PNES patient group did not vary between the patients who received or did not receive therapy and the absence of any significant difference in disease durations, we thought that antiepileptic drugs have a marked adverse effect on cognition.

Four patients in the epilepsy group in our study received topiramate therapy. No patients with epilepsy were using barbiturate. Neither drug was used in the PNES patient group. However, because multiple drug use was present in both patient groups and because of the low patient number, subgroup examinations could not be performed. It was therefore not possible to reveal which antiepileptic drugs affected cognition in this study.

Mood disorders are known to be common in both patients with epilepsy and those with PNES (32). It was foreseen that these variables may also have effects on cognitive abilities. Comparisons revealed that the HRSD scores of the patients with PNES were significantly higher than those of the patients with epilepsy. Analysis of the relation between the basal cognitive test scores and HRSD scores revealed a negative correlation in the patients with PNES between the high scale scores and cognitive test results. However, no similar relation was observed for the patients with epilepsy. In light of these findings, we think that mood disorders have a greater cognitive effect in patients with PNES.

This study determined the marked cognitive effects in both patients with epilepsy and those with PNES. Memory problems were more prominent and widespread in the patients with epilepsy subjected to analysis, whereas memory and executive problems were more prominent in the patients with PNES. The data obtained suggest that the effect of mood disorders on cognitive abilities were more intense in patients with PNES compared to those with epilepsy. The duration of disease was seen to have a negative effect on certain processes in both groups. The effects of antiepileptic drugs on cognition were revealed in patients with PNES, although it is impossible to state which drug groups have a more marked effect in this study. The foreseen adverse effect of seizures in the early stage on attention and executive functions in both patients with PNES and those with epilepsy did not emerge clearly.

The main limitation of this study is the low patient number and the fact that it was analyzed using non-parametric tests. Our patient number was lower than expected because of the long periods of hospitalization in the video monitoring unit.

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